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Advanced glycation end product accumulation: a new enemy to target in chronic kidney disease?

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Abstract

Purpose of review—The critical role of advanced glycation end products (AGEs) in the progression of chronic diseases and their complications has recently become more apparent. This review summarizes the recent contributions to the field of AGEs in chronic kidney disease (CKD).

Recent findings—Over the past 3 decades, AGEs have been implicated in the progression of CKD, and specifically diabetic nephropathy. Although numerous in-vitro and in-vivo studies highlight the detrimental role of AGEs accumulation in tissue injury, few prospective human studies or clinical trials show that inhibiting this process ameliorates disease. Nonetheless, recent studies have focused on the novel mechanisms that contribute to end-organ injury as a result of AGEs accumulation, as well as novel targets of therapy in kidney disease.

Summary—As the prevalence and the incidence of CKD rises in the United States, it is essential to identify therapeutic strategies that either delay the progression of CKD or improve mortality in this population. The focus of this review is on highlighting the recent studies that advance our current understanding of the mechanisms mediating AGEs-induced CKD progression, as well as novel treatment strategies that have the potential to abrogate this disease process.

Video abstract—http://links.lww.com/CONH/A12

Keywords

advanced glycation end products; chronic kidney disease

Introduction

Advanced glycation end products (AGEs) in the body can form endogenously or can be acquired from the environment. Endogenous formation results in part from the nonenzymatic reaction between reducing sugars and free amino groups of lipids and proteins, which was initially characterized as the browning reaction by the French chemist

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Maillard [1]. Although a limited formation of AGEs is part of normal metabolism, studies over the past century have characterized the detrimental effects of excess accumulation of these glycotoxins in nearly every organ system, including diabetes [2], neurodegenerative diseases [3], chronic pulmonary diseases [4], and rheumatological illnesses [5].

AGEs accumulation may also result from metabolism of excess glucose leading to glycolytic intermediates that increase the pool of reactive aldehydes and eventually AGEs. Although diabetes is the main cause of chronic kidney disease (CKD) worldwide, the accumulation of AGEs independent of hyperglycemia has been well documented [6■■]. Additionally, the consumption of a diet rich in foods cooked under dry and high-heat conditions has been shown to clearly contribute to an increase in the body AGE pool [7,8]. Regardless of whether the accumulation of AGEs is from an exogenous or endogenous source, glycotoxins, such as N-carbo-xymethyl-lysine, pentosidine, and methylglyoxal derivatives, are critical to the progression of CKD [9–11].

Potential strategies involving the restriction of exogenous sources of AGEs, reduction in formation of endogenous AGEs, antagonizing tissue effects of AGEs, and increasing the breakdown of existing AGEs have been the focus of recent studies. The available anti-age strategies in chronic kidney disease are as follows:

1. Restrict exogenous sources of AGEs:
    - **a.** Dietary restriction of AGEs (switch from high-heat, low-heat, and high-humidity cooking),
    - **b.** Inhibition of gastrointestinal absorption of dietary AGEs (increase dietary content, sevelamer carbonate, AST-120, lysozyme),
    - **c.** Reduce high-fructose intake.
2. Reduce endogenous AGEs formation:
    - **a.** Glycemic control,
    - **b.** Probiotics,
    - **c.** Antioxidants [Vitamin E, glutathione (GSH), lipoic acid(x005D),
    - **d.** (+/–)-2-isopropylidenehydrazono-4-oxo-thiazolidin-5-ylacetanilide (OPB-9195),
    - **e.** Thiamine derivatives (Benfotiamine),
    - **f.** Aminoguanidine,
    - **g.** BST-4997,
    - **h.** Angiotensin-converting-enzyme inhibitor (ACEI)/angiotensin receptor blockers (ARBs),
    - **i.** Hydralazine,
    - **j.** Linagliptin
    - **k.** Metformin,

l. Pioglitazone,

m. Pentoxyfylline,

n. Pyridoxamine,

o. Hexane extracts,

p. Quercetin,

q. 2-Dodecyl-6-methoxycyclohexa-2,5-diene-1,4-dion.

3. Increase breakdown of existing AGEs [alage-brium chloride (ALT-711)],

4. AGE receptor inhibitors [S100A12, pigment-epithelium derived factor (PEDF), DNA aptamers],

5. Kidney transplantation.

In this review, we discuss recent published advances in the understanding of the critical role of AGEs in patients with CKD, with a special emphasis on novel therapeutic targets on the horizon.

Excess Advanced Glycation End Products Contribute to End-Organ Damage in Chronic Kidney Disease

Regardless of hyperglycemia, oxidative stress in patients with diabetic nephropathy contributes to AGE formation [12■]. Miyata *et al.* [5] described the role of reactive carbonyl compounds as a contributing factor to the formation of AGEs in uremic patients, independent of hyperglycemia. Although an elevation in circulating AGEs is present in a predominant number of CKD patients, the progression to end-stage renal disease (ESRD) requiring dialysis is variable. A potential source of this variability may be secondary to polymorphisms in the receptor for AGE (RAGE), a receptor leading to activation of inflammatory pathways, and thereby con-tributing to the progression of CKD [13■■]. In a cohort of 174 European patients with stage 3 CKD, −374 T/A polymorphism was associated with elevated plasma levels of interleukin 6 and macrophage chemoattractant protein 1 (MCP1) [13■■]. In addition, patients who were carriers of this risk allele had increased albuminuria and worsened renal function by the end of the 84-month follow-up period [13■■]. The significant role of AGEs in contributing to end-organ damage in patients on chronic renal replacement therapy, hemodialysis or peritoneal dialysis was the focus of a recent review [14].

Several reviews have discussed in detail the deleterious role of AGEs in contributing to end-organ damage [14–19]. The accumulation of AGEs contributes to tissue injury by protein-crosslinking, thereby leading to alteration of protein structure and function and by activating proinflammatory and prooxidative cellular signaling pathways [20]. For instance, binding of AGEs to RAGE or toll-like receptor 2 and 4 initiates intracellular signaling and activates several inflammatory responses, contributing to oxidative stress [21]. In contrast, the AGE receptor 1 has marked antioxidant properties by regulating AGE/RAGE mediated activation

of nuclear factor kappa-B (NF-κB) [22], epidermal growth factor receptor, and extracellular receptor kinase [23,24].

The accumulation of AGEs also accelerates atherosclerosis via cross-linking of matrix proteins essential to endothelial function, platelet aggregation, and abnormal lipoprotein metabolism [25–27]. The oxidative modification of low-density lipoprotein (LDL) plays a vital role in atherosclerosis [28], and CKD patients have a higher serum concentration of glycated LDL [2], which is more prone to oxidation than nonglycated LDL [29]. In addition, glycated LDL is cleared from the circulation at a slower rate than nonglycated LDL [29]. Increased oxidation and reduced clearance of AGE-modified LDL may contribute to the increased rate of atherosclerosis observed in CKD patients. In a cross-sectional study from Poland, the authors investigated the relationship between plasma AGE levels and arterial stiffness (using pulse wave velocity) in CKD patients with and without diabetes [30]. Regardless of the cause of CKD, AGE levels correlated significantly with arterial stiffness, but diabetic CKD patients demonstrated the strongest relationship [30], suggesting an additive effect of hyperglycemia.

The mechanism by which early glomerular diseases, such as diabetic nephropathy, progress to interstitial fibrosis (i.e., advanced CKD) remains unresolved. Recent in-vitro studies revealed that exposure of tubular cells to AGEs results in the increased expression of transforming growth factor beta, plasminogen activator inhibitor-1, tissue transglutaminase, and MCP1 [31]. In addition, faster progression to diabetic nephropathy may correlate with elevated serum AGE levels [32■■]. Specifically, the authors showed that serum levels of methyl-glyoxal derivatives independently predicted a faster progression to diabetic nephropathy, as measured by increased glomerular basement thickness on electron microscopy [32■■]. Also, AGE-induced tubular damage in diabetic nephropathy seems to be mediated by sodium-glucose cotransporter 2 in the apical membrane of proximal tubular cells as inhibiting the expression of sodium-glucose cotransporter 2 abrogated AGE-mediated apoptosis of cultured proximal tubular cells [33].

Several studies have highlighted the association between elevated serum AGEs and cardiovascular morbidity in CKD using left ventricular (LV) mass as a surrogate marker [34]. A cross-sectional study, involving 142 Italian CKD patients, revealed that soluble RAGE levels, a supposed inhibitor of RAGE, inversely correlated with LV mass and C-reactive protein (CRP) levels [35]. In another recent study, the authors found that soluble RAGE correlated strongly with less LV dysfunction [36]. However, these findings have been contradicted in a small pediatric cohort, in which plasma AGE levels did not correlate with a proinflammatory state in patients with CKD [37]. This lack of correlation was also observed with serum AGE levels and LV hypertrophy [38].

Endothelial dysfunction is an important factor in the progression of diabetic nephropathy. In addition to the critical role of AGEs in the later stages of diabetic nephropathy, the accumulation of AGEs contributes to the initial endothelial injury. For instance, inhibitors to nitric oxide synthase, such as asymmetric dimethylarginine (ADMA), are strongly associated with increased AGE levels in ESRD patients with endothelial dysfunction [39].

Exposure to AGEs increased ADMA levels in cultured endothelial cells, by inhibiting the enzyme critical for ADMA degeneration, thereby contributing to endothelial injury [39].

Skin is another common site, in which excess AGEs result in cross-linking of collagen and initiate intracellular pathways that result in increased oxidative stress. A recent review highlights the potential use of skin autofluorescence as a marker of AGE accumulation in CKD patients with or without diabetes [40■]. Skin biopsies have validated that an increase in skin autofluorescence strongly correlates with an accumulation of pentosidine, N-carboxymethyl-lysine, and carboxyethyl lysine levels in the skin. Interestingly, using skin autofluorescence as a marker of excess AGEs may possibly serve as a better marker of tissue damage than plasma AGE levels. For instance, an increase in skin autofluorescence positively correlated with carotid intima-medial artery thickness and diastolic dysfunction, but inversely correlated with endothelial progenitor function in CKD patients, whereas serum pentosidine only correlated with carotid intima-medial artery thickness [40■]. Recent in-vitro studies revealed that AGEs, at the concentrations observed in CKD patients, did not induce endothelial progenitor cell apoptosis, contrary to previous studies [41]. A potential hypothesis to explain this discrepancy is that, in contrast to tissue bound AGEs, circulating AGEs are constantly turning over and serial plasma measurements may be required for proper quantification of circulating levels.

Limiting the Exogenous Sources of Advanced Glycation End Products

Several studies have examined the beneficial role of minimizing the excessive intake of AGEs [42–44]. Dietary AGE intake is easily reduced by changing the method of cooking from a high dry-heat application to a low heat and high humidity, independent of its nutrient composition [45,46]. Restricting excess dietary AGE intake protects against a loss of innate immunity [44] and attenuates diabetic angiopathy and nephropathy [42,43]. Several of these anti-AGE strategies have been evaluated in recent years (Table 1) [47,48,49■■,50].

Minimizing the accumulation of exogenous AGEs in CKD patients can also be accomplished by inhibiting the absorption of dietary AGEs in the gut. Although primitive, increasing dietary fiber content attenuates the increase in AGEs and slows the progression of CKD. For instance, consumption of a high-fiber diet, such as oats, in rats slowed the progression of diabetic nephropathy with a concurrent reduction in RAGE and NF-κB levels [51]. Sevelamer carbonate, a nonabsorbed phosphate-binding polymer, is frequently used in CKD patients to decrease serum phosphate levels [52,53]. A recent single-center, randomized, open-label crossover study compared the role of sevelamer carbonate with calcium carbonate in diabetic CKD patients (stage 2–4) in the accumulation of excess circulating AGE levels and inflammatory markers. Results revealed a significant reduction in serum AGEs, HbA1c, and markers of inflammation and oxidative stress in patients receiving sevelamer [47]. Antioxidant markers, such as AGER1 and SIRT1 mRNA levels, also markedly improved in the sevelamer group independent of serum phosphate levels. In addition, recent studies reveal that RAGE-based bio-adsorbent devices were effective at lowering AGEs by 50% from serum collected from patients with ESRD [54■■]. However, the specificity of these bioadsorbents, as well as their long-term efficacy and safety, remains to be determined.

Methylglyoxal derivatives, a major precursor of AGE formation, are a reactive dicarbonyl formed from the metabolism of fructose and glucose. A diet rich in high-fructose corn syrup has been associated with the progression of diabetes and hypertension. Recent studies demonstrated that rodents exposed to a high-fructose diet for 4 months exhibited an increase in serum levels of methylglyoxal derivatives, angiotensin II, renin, and blood pressure [55], whereas glutathione levels were significantly suppressed. Interestingly, in addition to the increased serum AGE levels, RAGE and NF-κB levels were specifically increased in aortaof rodents fed the high-fructose diet [55]. Furthermore, the formation of AGEs appears to mediate high-fructose diet-induced nonalcoholic fatty liver disease [56]. With the increased consumption of beverages rich in fructose in the past decade, the role of a high-fructose diet in the accumulation of endogenous AGEs cannot be neglected.

Limiting the Endogenous Formation of Advanced Glycation End Products in Chronic Kidney Disease

In addition to minimizing the intake of excess AGEs, limiting the endogenous formation of AGEs is also central to therapy. As diabetes is a major contributor to AGE formation, strict glycemic control can minimize the formation of AGEs and has been the focus of other reviews [57■]. Other therapeutic strategies have been identified in reducing the formation of endogenous AGEs, including the use of antioxi-dants, such as vitamin E, GSH, and lipoic acid [27,58]. In addition, the use of liposoluble thiamine derivatives, such as benfotiamine, has previously been shown to inhibit the formation of AGEs and reduce kidney injury in diabetic murine models [59,60]. Other agents, such as aminoguanidine, a nucleophile hydrazine group that binds to carbonyl groups and prevents cross-linking, have shown to be effective in lowering serum AGEs [61,62], but adverse reactions have also been documented [17,63,64]. Similar to aminoguanidine, OPB-9195, a thiazolidine derivative, binds to carbonyl groups and prevents cross-linking to proteins. Administration of OPB-9195 reduced the formation of pen-tosidine and the thickening of the neointimal layer in a rat model of carotid artery injury [65]. Although animal studies were promising, studies in humans have not shown this favorable effect [66,67].

Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers have shown to reduce the production of reactive carbonyl precursors for AGE formation [68–71]. More recently, in-vitro studies, involving cultured mouse podocytes, revealed that exposure to telmisartan attenuates DNA damage in the podocyte and inhibits cell detachment [39]. Also, in-vitro studies demonstrate that hydralazine, an antihypertensive agent, can reduce AGE formation by trapping reactive carbonyl compounds, leading to the modification of oxidative metabolism [72]. Hydralazine was also recently shown to reduce protein glycation with a reduction in RAGE, NADPH oxidase, and superoxide dismutase levels [73] in a murine model of diabetic nephropathy. In addition, inhibiting dipeptidyl peptidase-4, an enzyme that degrades incretins that promote insulin release and slow gastric emptying, has been shown to reduce AGE-mediated oxidative stress [74]. The use of linagliptin, dipeptidyl pepti-dase-4 inhibitor, blocks AGE-mediated oxidative stress in cultured endothelial cells and reduces AGE levels, RAGE expression, and oxidative stress in diabetic rats [74]. A reduction in

albuminuria was also observed in the diabetic mice treated with lina-gliptin, suggesting a potential therapeutic option in early diabetic nephropathy [74].

Repurposing of currently used medications, including metformin, pioglitazone, and pentoxy-fylline to inhibit formation of AGEs, has been described [75]. For instance, metformin and piogli-tazone reduce serum pentosidine levels significantly in diabetic patients [48]. In addition, pyridoxamine, a known AGE inhibitor, was recently demonstrated to be superior to metformin in inhibiting glycation at early, intermediate, and late stages of AGE formation [6■■]. However, the role of these compounds in CKD remains to be clearly delineated.

For the past 20 years, animal studies have shown that blocking RAGE reduced oxidative stress and attenuated endothelial dysfunction [76]. Novel agents targeting the RAGE receptor are being developed to treat diabetic vascular complications [77]. Elevated serum levels of the RAGE ligand, S100A12, are associated with mortality [78]. Consequently, strategies to inhibit S100A12 may reduce the accumulation of AGEs, as well as curb the progression of CKD. Potential therapeutic targets are currently being investigated in targeting pathways that lead to degradation of AGEs, such as methyl-glyoxal derivatives. Methylglyoxal derivatives have been implicated in endothelial dysfunction and the development of vascular complications in patients with CKD. Recently, using murine models of diabetic nephropathy, the overexpression of glyoxa-lase-I, which normally catabolizes methylglyoxal derivatives, reduced oxidative stress, and attenuated glomerular injury and endothelial dysfunction [79]. However, further validation will be required before it is evaluated as a potential clinical therapeutic target.

The use of alternative medicine in inhibiting the formation of AGEs is on the horizon. For instance, the use of hexane extracts from the leaves of the plant, *Piper auritum*, inhibited the formation of AGEs and limited oxidative stress in cell culture and in a murine model of diabetic nephropathy [80]. Similarly, the use of quercetin from leaf extracts of the plant, *Allium victorialis*, inhibited AGEs formation in cultured mouse kidney mesangial cells [81]. The oral administration of 2-dodecyl-6-methoxycyclohexa-2,5-diene-1,4-dione from the roots of the plant, *Averrhoa carambola*, has shown to be effective in attenuating AGEs formation and progression of kidney disease in diabetic mice [82]. Recent studies from Japan revealed that PEDF, a serine protease inhibitor, attenuated AGE-induced apoptosis by suppressing the expression of RAGE [83]. PEDF limited reactive oxygen species generation by activating peroxisome proliferator-activated receptor gamma (PPAR-γ), a known inhibitor of inflammatory pathways [83]. However, further studies are required to validate these findings and to determine whether there is a functional and his-tological improvement in kidney disease with their use.

The critical role of the microbiome in regulating various cellular processes has been in the forefront of science in the past few years. Recent studies suggest that the accumulation of AGEs in CKD patients may potentially be mediated by the altered microbiome in these patients [84■■]. Specifically, treatment with probiotics has shown to reduce markers of oxidative stress, uremic toxins, and attenuate CKD progression [84■■].

More recently, the use of high-affinity DNA aptamers, single-stranded molecules that bind with high affinity to target proteins, was characterized in diabetic nephropathy [85]. Elevated levels of glomerular RAGE, MCP1, connective tissue growth factor, and type IV collagen are typically observed in diabetic mice, which were blocked after infusion with DNA aptamers targeting AGEs specifically [85]. In addition, histological and functional improvement was observed with aptamer use [85]. Although promising, the effects of nonspecific interactions with aptamers need to be further investigated.

Statins do provide benefit to patients with CKD [86], but the mechanism mediating this process remains unclear. Recent studies from Japan reveal that statins may attenuate tubular injury by reducing the levels of RAGE [87]. In AGE-treated cultured proximal tubular cells, pravastatin inhibited RAGE levels, reactive oxygen species (ROS) generation, and apoptosis in a dose-dependent manner. These findings were also confirmed with rosuvastatin use [87], thereby suggesting that the mechanism by which statins attenuate the progression of CKD is by inhibiting the formation of AGEs. However, this beneficial effect of statins is lost in patients on chronic dialysis, thereby placing doubt on the proposed mechanism.

In comparison to dialysis, kidney transplantation provides a clear survival advantage to patients with advanced CKD [88]. After kidney transplantation, many factors may contribute to the improvement in cardiovascular morbidity and overall survival advantage in these patients. Using skin autofluorescence showed that tissue AGE levels were markedly improved in patients postkidney transplant, as compared with patients on dialysis [49■■]. In this cohort of 66 postkidney transplant, 1707 CKD, and 115 dialysis patients, mean skin autofluorescence levels were signficantly lower in the kidney transplant patients than in the patients on dialysis. However, the levels were similar between posttransplant patients and patients with less advanced CKD (stage 3) [49■■].

Conclusion

Recent published data reaffirm the critical role of AGEs in the progression of CKD and its complications. In addition, studies from the past year reveal that more novel therapeutic agents are on the horizon. However, we still remain far from the potential use of these agents in clinical practice. With the burden of a burgeoning CKD population worldwide, there is a dire need to identify mechanisms and therapeutic strategies that halt the progression of kidney disease.

Acknowledgments

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Key Points

- Independent of hyperglycemia, the tissue accumulation of AGEs contributes to the progression of diabetic nephropathy.
- Skin autofluorescence may serve as a potential diagnostic tool for quantifying the tissue accumulation of AGEs, and thereby serve as a surrogate marker of end-organ damage.
- Current therapeutic targets focus on either limiting the consumption of exogenous AGEs or inhibiting the formation of AGEs.
- Excess consumption of high-fructose corn syrup is associated with increased serum AGE levels and tissue accumulation of AGEs.

Table 1

Recent clinical studies involving anti-advanced glycation end product strategies in chronic kidney disease

Anti-AGE strategy	Reference	Study type	*N*	Primary end-points
Sevelamer carbonate	[47]	Single-center, open-label RCT	20	Serum AGE levels, markers of oxidative stress and inflammation
Metformin, pioglitazone	[48]	Open-label RCT	66	Serum HbA1c, pentosidine levels
Kidney transplantation	[49■■]	Cross-sectional study	1888	Skin autofluorescence
Sevelamer carbonate	[50]	Multicenter RCT	183	Serum pentosidine levels, coronary artery calcification score

AGE, advanced glycation end product; HbA1c, hemoglobin A1c; RCT, randomized controlled trial.